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On the Reaction of Diphthaloyl-DL-lysine Chloride with Dibenzyl Sodiomethylmalonate. Preparation of DL-4,8-Diamino-3-octanone

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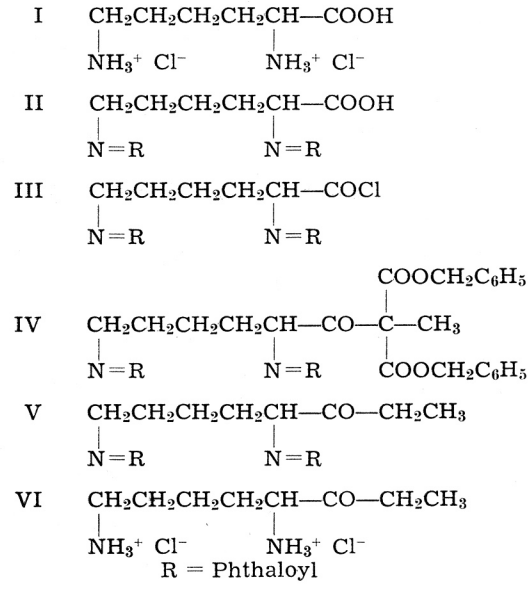
The applicability of the Bowman ketone synthesis to diamino acids has been demonstrated. Thus, diphthaloyl-DL-lysine chloride (III) was condensed with dibenzyl sodiomethylmalonate yielding DL-4,8-diphthalimido-3-octanone (V). The latter gave by hydrolysis DL-4,8-diamino-3-octanone (VI).

A special case of the Bowman ketone synthesis[1,2] is represented by its extension to α-monoamino acids as acylating components, which was demonstrated recently on several examples. The synthesis is available also for the preparation of α-amino ketones, amino alcohols and α-diamines as well as for the solution of certain configurational questions[3–7].

It seemed therefore desirable to extend the method to aliphatic diamino acids such as lysine inasmuch as the expecting ketone might be of interest as convenient intermediate in the possible synthesis of hemlock alcaloids. For this purpose DL-lysine dihydrochloride was converted into the diphthaloyl



derivative (II) by refluxing its glacial acetic acid solution with phthalic anhydride in the presence of pyridine. The addition of pyridine is essential, otherwise no defined product could be obtained. The diphthalimido acid chloride (III) was condensed with dibenzyl sodiomethylmalonate and the resulting crude β-keto ester (IV) converted into crystalline DL-4,8-diphthalimido-3--octanone (V). The ketone was characterized as 2,4-dinitrophenylhydrazone. When V was submitted to acid hydrolysis, the phthaloyl groups were split off and DL-4,8-diamino-3-octanone (VI) was obtained. The ketone VI was characterized as dihydrochloride and 2,4-dinitrophenylhydrazone dihydrochloride. We have also attempted the acylation of dibenzyl sodiomethylmalonate with DL-2-phthalimido-6-benzamidocaproic acid, but the expected ketone V could not be isolated.

EXPERIMENTAL

The melting points are uncorrected.

Dibenzyl methylmalonate

To a well stirred suspension of powdered sodium (10.12 g., 0.44 mole) in benzene (150 ml.) absolute ethanol (40 ml.) was added. After the initial reaction has subsided the mixture was refluxed until all sodium was dissolved. A solution of diethyl malonate (70.5 g., 0.44 mole) in benzene (150 ml.) was then added dropwise with vigorous stirring. The reaction mixture became viscous and yellow. A solution of benzyl alcohol (95 g., 0.88 mole) in benzene (100 ml.) was added to the above mixture while stirring and the excess of ethanol was removed azeotropically as a binary mixture with benzene. After addition of methyl iodide (62.5 g., 0.44 mole) the mixture was refluxed for 6 hrs. Water (150 ml.) was then added, the benzene layer separated and the aqueous layer twice extracted with benzene. The combined benzene extracts yielded by distillation 67 g. (51%) colorless oil, b. p. 130—140°/0.02 mm. A sample for analysis was redistilled *in vacuo*.

Anal. 9.360 mg. subst.: 24.85 mg. CO_2, 5.25 mg. H_2O
$C_{18}H_{18}O_4$ (298.32) calc'd: C 72.47; H 6.08%
found: C 72.45; H 6.28%

Diphthaloyl-DL-lysine (II)

DL-Lysine dihydrochloride (I) (13 g., 59 mM) prepared according to Eck and Marvel[8], and phthalic anhydride (28.03 g., 188 mM) were dissolved in glacial acetic acid (250 ml.) and refluxed in the presence of pyridine (25 ml.) for 3 hrs. The solution was then poured into ice-water (1000 ml.), the separated crystals filtered by suction and recrystallized from a mixture of 96% ethanol — water (1 : 1). The yield was 18.2 g. (75%), colorless needles, m. p. 169—170°. For analysis the substance was recrystallized once more; m. p. 170°. Wanag and Verbergs[9] give the m. p. 170° for active diphthaloyl-L-lysine.

Anal. 9.065 mg. subst.: 21.72 mg. CO_2, 3.50 mg. H_2O
6.665 mg. subst.: 0.421 ml. N_2 (22°, 743 mm)
$C_{22}H_{18}O_6N_2$ (406.38) calc'd: C 65.02; H 4.47; N 6.89%
found: C 65.38; H 4.32; N 7.15%

Diphthaloyl-DL-lysine Chloride (III)

Ten grams (23.5 mM) of II and thionyl chloride (30 ml.) were refluxed for 1 hr. The excess of thionyl chloride was distilled off *in vacuo* at 70° and the last traces were removed azeotropically with three 30 ml. portions of benzene. The viscous, yellow oil (10.98 g.) was obtained and used in the next step without further purification.

DL-*4,8-Diphthalimido-3-octanone* (V)

To 593 mg. (25.8 mM) of sodium powder in benzene (50 ml.) a solution of dibenzyl methylmalonate (7.71 g., 25.8 mM) in benzene (50 ml.) was added at room temperature with continuous stirring. The mixture was refluxed until all sodium was dissolved and then cooled to room temperature. A solution of III (10.98 g., 25.8 mM) in benzene (50 ml.) was then added and stirring continued for 12 hrs. The reaction mixture was poured into ice-water containing a few drops of concentrated sulphuric acid. The benzene layer was washed with water and the solvent evaporated *in vacuo* at 40—50°. The oily residue, insoluble in ethanol, was dissolved in dioxane (50 ml.) and hydrogenated in the presence of 1 g. of 10% palladium on barium sulphate catalyst at room temperature and at atmospheric pressure. Two more 1 g. portions of the catalyst were added to the filtered solution when the hydrogen absorption ceased. The hydrogen uptake was 885 ml. (calc'd. 1158 ml. at 0° and at 760 mm) after 45 hrs. The catalyst was filtered off and the yellow filtrate decarboxylated by refluxing it for 2 hr. After evaporation of the solvent to dryness the resulting oil was heated for additional 1 hr. at 100° *in vacuo*. The oily residue (9.7 g.) was taken into 50 ml. of benzene and chromatographed on activated alumina (Riedel-de Haën). The combined benzene eluates gave 3.39 g. (31.4%) of a viscous, pale yellow oil which was dissolved in 96% ethanol and the solution allowed to stand at room temperature for two weeks. The separated prismatic crystals were collected; m. p. 90—91°. For analysis the substance was recrystallized from dioxane.

Anal. 8.250 mg. subst.: 20.64 mg. CO_2, 4.03 mg. H_2O
5.890 mg. subst.: 0.358 ml. N_2 (21°, 749 mm)
$C_{24}H_{22}O_5N_2$ (418.43) calc'd: C 68.73; H 5.30; N 6.69%
found: C 68.69; H 5.50; N 6.95%

2,4-Dinitrophenylhydrazone. — To the solution of the crude, oily ketone V (418 mg., 1 mMole) in 10 ml. of 96% ethanol 2,4-dinitrophenylhydrazine (238 mg., 1,2 mMole) in 10 ml. of 96% ethanol was added and refluxed for 10 minutes. After cooling 5 drops of concentrated hydrochloric acid were added to the solution and it was refluxed for additional 2 minutes. From the cooled solution 470 mg. crystals separated, m. p. 100—105°, which were recrystallized from 96% ethanol containing some hydrochloric acid. Orange needles, m. p. 104—105°.

Anal. 9.495 mg. subst.: 20.87 mg. CO_2, 3.79 mg. H_2O
3.940 mg. subst.: 0.496 ml. N_2 (24°, 755 mm)
$C_{30}H_{26}O_8N_6$ (598.56) calc'd: C 60.19; H 4.38; N 14.04%
found: C 59.98; H 4.47; N 14.37%

DL-*4,8-Diamino-3-octanone* (VI)

A sample of V (500 mg., 1.19 mM) and 6 *N* hydrochloric acid (20 ml.) were refluxed for 24 hrs. Phthalic acid (336 mg., yield 84.7%, m. p. 194°) crystallized on cooling, the filtrate was extracted with ether and the aqueous layer evaporated *in vacuo* to dryness. In this manner crude, oil 4,8-*diamino*-3-*octanone* dihydrochloride (310 mg.) was obtained.

2,4-Dinitrophenylhydrazone dihydrochloride. — The crude ketone (270 mg., 1.29 mM) was dissolved in absolute ethanol (5 ml.) and a solution of 2,4-dinitrophenylhydrazine (281 mg., 1.4 mM) in absolute ethanol (10 ml.) was added. Further procedure was closely similar to that described in the precedent preparation. The yield was 342 mg. (64.5%), m. p. 214—215°. For analysis the substance was recrystallized from boiling ethanol containing some hydrochloric acid; yellow needles, m. p. 216—217°.

Anal. 6.335 mg. subst.: 9.54 mg. CO_2, 3.29 mg. H_2O
4.175 mg. subst.: 0.755 ml. N_2 (23°, 749 mm)
$C_{14}H_{24}O_4N_6Cl_2$ (411.29) calc'd: C 40.88; H 5.88; N 20.44%
found: C 41.09; H 5.81; N 20.55%

DL-2-Phthalimido-6-benzamidocaproic Acid

A finely ground mixture of DL-2-amino-6-benzamidocaproic acid (6 g., 23.9 mM), prepared according to Eck and Marvel[8], and phthalic anhydride (3.55 g., 23.9 mM) was heated with occasional stirring in an oil bath at 130—140°. After cooling the melt was disolved in 96% ethanol (100 ml.) and water was added drop by drop until the solution became slightly turbid. The solution was allowed to crystallize overnight in the refrigerator. Colorless crystals (8 g., yield 88%), m. p. 161—162°. Further crystallizations did not raise the melting point.

Anal. 8.735 mg. subst.: 21.21 mg. CO_2, 4.08 mg. H_2O
7.475 mg. subst.: 0.482 ml. N_2 (24°, 742 mm)
$C_{21}H_{20}O_5N_2$ (380.39) calc'd: C 66.30; H 5.30; N 7.37%
found: C 66.26; H 5.23; N 7.24%

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IZVOD

O reakciji klorida diftaloil-DL-lizina s dibenzil natrium-metil-malonatom. Pripravljanje DL-4,8-diamino-3-oktanona

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Pokazano je, da se Bowmanova ketonska sinteza može protegnuti i na diaminokiseline. Kondenzacijom klorida diftaloil-DL-lizina (III) s dibenzil natrium-metil-malonatom dobiven je DL-4,8-diftalimido-3-oktanon (V). Hidrolizom sa solnom kiselinom V je preveden u DL-4,8-diamino-3-oktanon (VI), koji je karakteriziran kao 2,4-dinitrofenilhidrazon-dihidroklorid.

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